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10/620,148	07/14/2003	Yoshihiro Yoshihara	382.1031CON	2595

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EXAMINER	
HAMA, JOANNE	

ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/620,148	YOSHIHARA, YOSHIHIRO	
	Examiner	Art Unit	
	Joanne Hama, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,6,7,11,12 and 21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,6,7,11,12 and 21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant filed a response to the Final Rejection of January 11, 2006 on June 21, 2006. Claims 4, 5, 8-10,13-20 are cancelled. Claim 1 is amended. Claim 21 is new.

Claims 1-3, 6, 7, 11, 12, 21 are under consideration.

While the Examiner has written a Final Action on January 11, 2006, new considerations are being raised as follows. Thus, the finality of the Final Action has been withdrawn.

Priority

Applicant indicates that a petition to revive parent application No. 09/763,117 was granted and that a copy of the decision is enclosed with the instant response. The Examiner acknowledges the copy of the decision and acknowledges that the instant application has priority to U.S. Application 09/763,117, filed February 15, 2001, now abandoned and PCT/JP99/04439, filed August 19, 1999, and foreign priority to Application 232817, filed August 19, 1998, filed in Japan.

Oath/Declaration

Because Applicant has established priority to U.S. Application 09/763,117, PCT/JP99/04439, and Japanese patent application 232817, the objection to the oath/declaration is withdrawn.

Withdrawn Rejections

35 U.S.C. § 112, 1st parag. Enablement

Applicant's arguments, see page 4 of Applicant's response, filed June 21, 2006, with respect to the rejection of claims 1-4, 6, 7, 11, 12 have been fully considered and are persuasive. Applicant has amended claim 1 to include the word, "mammalian" to describe the neuron specific promoter. The rejection of claims 1-3, 6, 7, 11, 12 has been withdrawn. It is noted that the rejection of claim 4 is withdrawn as claim 4 is cancelled.

35 U.S.C. 102 (b)

Applicant's arguments, see pages 4-5 of Applicant's response, filed June 21, 2006, with respect to the rejection of claims 1-4, 6, 7, 11, 12 as being anticipated by Yoshihara, International Application No. PCT/JP99/04439 have been fully considered and are persuasive. Applicant has perfected the priority of the instant application (see above). The rejection of claims 1-3, 6, 7, 11, 12 has been withdrawn. It is noted that the rejection of claim 4 is withdrawn as claim 4 is cancelled.

Applicant's arguments, see pages 4-5 of Applicant's response, filed June 21, 2006, with respect to the rejection of claims 1-4, 6, 7, 11, 12 as being anticipated by Yoshihara et al., 1999, Neuron, have been fully considered and are persuasive. Applicant has perfected the priority of the instant application (see above). The rejection of claims 1-3, 6, 7, 11, 12 has been withdrawn. It is noted that the rejection of claim 4 is withdrawn as claim 4 is cancelled.

35 U.S.C. 103(a)

Applicant's arguments, see pages 4-5 of Applicant's response, filed June 21, 2006, with respect to the rejection of claims 1-4, 6, 7, 11, 12 as being anticipated by Yoshihara et al., 1999, Neuron, have been fully considered and are persuasive. Applicant has perfected the priority of the instant application (see above). The rejection of claims 1-3, 6, 7, 11, 12 has been withdrawn. It is noted that the rejection of claim 4 is withdrawn as claim 4 is cancelled.

New/Maintained Rejections

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-4, 6, 7, 11, 12 are newly rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible, specific and substantial utility or a well established utility. According to the Revised Utility Examination Guidelines, see the Federal Register, Vol. 66, No. 4, pp. 19092-1099 (January 5, 2001), also available at http://uspto.gov/web.menu.utility.pdf, the following definitions of credible, specific, and substantial apply.

A credible utility is one that a person of ordinary skill in the art would accept as currently available. An assertion is considered credible unless (a) the logic underlying the assertion is seriously flawed, or (b) the facts upon which the assertion is based are

inconsistent with the logic underlying the assertion. Credibility as used in this context refers to the reliability of the statement based on the logic and facts that are offered by the Applicant to support the assertion of utility. A credible utility is assessed from the standpoint of whether a person of ordinary skill in the art would accept that the recited or disclosed invention is currently available for such use.

A specific utility is one that is specific to the subject matter claimed. This contrasts with a general utility that would be applicable to the broad class of the invention.

A substantial utility is one that defines a real world use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a real world context of use are not substantial utilities. Research that involves studying the properties of the claimed product itself does not constitute a substantial utility.

See also MPEP 2107-2107.02, and *Brenner, Comr. Pats. v. Manson*, 148 USPQ 689 (US SupCt 1966).

The instant claims are drawn to a transgenic mouse whose genome comprises a nucleotide sequence encoding a trans-synaptic tracer protein operably linked to a mammalian neuron-specific promoter, wherein the trans-synaptic protein is expressed in neurons of interest. The claims are also drawn to a cultured neuron obtained from the transgenic mouse and to a method of using the cultured neuron in a method of screening for substances that have an effect upon cultured neurons. The specification identifies the following uses for the claimed mice and cells: 1) the transgenic mice are useful for the elucidation of causes for various neurogenic diseases and for the

establishment of medical treatment for those diseases, wherein the transgenic mice may be crossed with an animal model for disease resulting from abnormal neural pathways or with a spontaneously mutated animal model, 2) the transgenic mouse may be used to create an artificial pathological model for diseases such as Parkinson's disease, ischaemia, head injury or various mental diseases for the analysis of injured pathways or compensatory pathways, 3) the transgenic animal may be used to assess the potency of administered drugs (e.g. the trans-synaptic protein can be used to trace cells for the ability to restore injured pathways or to form compensatory pathways), and 4) the cells obtained from the transgenic mice may be cultured to create cultured neurons that express the trans-synaptic protein, which may then be used to screen for drugs that affect cell survival and maintenance, dendrite extension, synapse formation, various enzymatic activities, and/or neurotransmitter production (specification, pages 4-5).

In regards to asserted utility 1), as identified above, the stated utility of the mice used to elucidate the causes of various neurogenic diseases and for the establishment of medical treatment for diseases does not constitute a real world utility and therefore is not a substantial utility, but rather represents further research on the produce to identify or reasonably confirm a real world utility. As stated in the Guidelines set forth above, research that involves studying the properties of the claimed product itself does not constitute a substantial utility. Further, such an asserted utility constitutes a general, rather than a specific, utility as all transgenic mice comprising a reporter gene can be used to identify cells. It is understood that the claimed mice are unique in that the trans-

synaptic tracer protein can be used to determine secondary and tertiary cells that are related to the original neuron secreting the trans-synaptic tracer protein. However, determining a network of neurons does not elucidate diseases nor does it help establish medical treatment for disease. Therefore, asserted utility 1) does not meet the standard for a specific and substantial utility.

In regards to asserted utility 2), as identified above, the specification fails to demonstrate that expressing any trans-synaptic protein in a transgenic mouse would result in any pathological models. While the specification teach that a mouse comprising a pL7-tWGA construct and a mouse comprising a pOMP-tWGA construct were made (specification, Examples 2 and 3), the specification does not teach that these mice are a model for any disease or disorder. As such, it is unclear how the claimed mice have any of asserted utility 2).

With regard to asserted utility 3), as identified above, while the transgenic mice may be used to determine the potency of administered drugs, the asserted use is a general, rather than a specific, utility because transgenic mice comprising a reporter gene can be used to identify cells. As such, determining neural networks affected by administered drugs using the claimed mice is a general and not a specific and substantial use of the claimed mice.

With regard to asserted utility 4), as identified above, because the claimed mice have no specific and substantial utility, the cultured cells obtained from the claimed mice have no utility. While the cultured cells can be used to screen for drugs, screening for drugs using cultured cells comprising a reporter gene construct has the same general

utility of a cultured non-transgenic cell. That is, while the trans-synaptic tracer protein helps an artisan visualize a network of cells in a dish, the claimed cell behaves no differently from a wild-type cell, upon treatment of either cell with drugs. As such, the specific and substantial use of the claimed cell is not apparent.

Thus, in view of the discussion above, the skilled artisan would not find any of the asserted utilities of the transgenic mouse, cells derived from the mouse, and methods of using the claimed cells to be specific and substantial, or well-established.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 6, 7, 11, 12 are newly rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed

invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

As discussed above in the utility rejection, while it is understood that the claimed mice and cells obtained from the mice facilitate a system used to visualize a network of neuronal cells, the specification does not provide guidance for a specific and substantial use of the claimed mouse or cell wherein expression of the trans-synaptic tracer protein has a particular biological effect that distinguishes it from a wild-type cell. This issue of "biological effect" is an important issue with regard to utility and enabled use of the claimed invention, as follows.

With regard to the claims being drawn to a method for screening for substances having an effect upon cultured neurons (claim 21), the method entails taking cultured cells from the claimed transgenic mouse, treating a set of cultured cells with a test substance, and comparing the effect of a test substance on the expression level of the trans-synaptic tracer protein in cells that received the test substance with cells that did

not receive the test substance. While the specification teaches that a trans-synaptic tracer protein is envisioned to include, but not limited to, Concanvalin A agglutinin (ConA), Pisum sativum agglutinin (PSA), Lens Culinaris (LCA) (specification, page 3), the specification does not teach what relationship there is between these trans-synaptic tracer proteins and a biological effects exhibited in a cell, including cell survival and maintenance, dendrite extension, synapse formation, enzymatic activity, and neurotransmitter production, such that when expression levels of the trans-synaptic protein changes, the changes would indicate the effect of the test substance. As the claim reads, the method is an assay to find test substances that affect the expression level of the trans-synaptic tracer protein. This means, the screen is used to identify test substances that a) alter the promoter that drives expression of the trans-synaptic tracer protein, b) alter the rate of mRNA encoding trans-synaptic tracer protein being made, c) alter the rate that the mRNA encoding trans-synaptic tracer protein is being translated in the ER, d) alter the rate that the trans-synaptic protein is being post-translationally modified such that it can be incorporated into secretory vesicles, e) changes in secretion caused by changes in the secretory vesicle, or f) changes in the ability of a secondary neuron to take up the trans-synaptic tracer protein. While this assay, particularly for points a-d, would provide information relative to the trans-synaptic tracer protein, the assay does not provide guidance for an artisan to elucidate causes for various neurogenic diseases or establish medical treatment for those diseases, nor does it provide a way of making any artificial pathological model for a neurological disease or disorder. This is because nothing in the art or the specification establishes a

relationship between the trans-synaptic protein and any disease, disorder, or neurological process. Similarly, with respect to claim 7, wherein the effect of the test substance is an effect chosen from among the group consisting of effect upon cell survival and maintenance, dendrite extension, synapse formation, enzymatic activity, and neurotransmitter production, the specification does not provide guidance as to how affecting the expression levels of trans-synaptic tracer protein would result in these phenotypes.

With regard to e) and f), the specification does not teach an artisan how to discriminate that the changes in trans-synaptic tracer protein levels in the synaptic cleft is a result of changes from a)-d) and/or resulting from changes in the synaptic vesicle and/or resulting from changes in the ability of the secondary neuron to take up the trans-synaptic tracer protein. With regard to changes in the synaptic vesicles, no guidance is provided that this is what is envisioned by the claimed invention. Further, the art teaches that neurons have a defect in making synaptic vesicles die. For example, the art teaches neurons that have defect in KIF1A, a protein implicated in transport of synaptic vesicle precursors, fail to receive afferent stimulation, such as neuronal contacts or neurotransmission, and result in cell death (Yonekawa et al., 1998, Journal of Cell Biology, 141: 431-441, abstract). As this teaching applies to the instant invention, when an artisan is detecting the trans-synaptic tracer protein (e.g. by immunocytochemistry) and fails to see any neurons positive for the protein, it is unclear whether the lack of protein is because of a defect in vesicle formation or is a result of an unrelated pathway stimulating the apoptotic pathway. As such, to identify secretory

defective neurons cannot be accomplished using the claimed cells. With regard to changes in the uptake system of the secondary neuron, the specification does not indicate that this is what was envisioned at the time of filing. In addition to this, with regard to the reduced or increased ability of a neuron to take up a trans-synaptic protein, it is unclear how uptake of this protein is related to or is indicative of a biological phenomenon such that using this aspect of the assay has specific biological use.

It should also be pointed out that specific support in looking for substances that change synaptic vesicle release and uptake by a neuron receiving the trans-synaptic tracer protein was not envisioned at the time of filing as the specification teaches that, "(a)s used in the transgenic animals of the present invention, the term 'specific' or 'specifically' means that the trans-synaptic tracer protein is sufficiently expressed to distinguish particular neurons from other cells when it is visualized with an enzyme-labelled antibody, etc., but it does not necessarily mean that no trans-synaptic tracer protein is expressed in any other cell (specification, page 3, 3rd parag. under "Disclosure of the Invention")." With particular attention to the phrase, "but it does not necessarily mean that no trans-synaptic tracer protein gene is expressed in any other cell," the phrase could be readable as broadly as using a pan-neuronal promoter. The phrase does not establish a limitation that in order to detect changes in vesicle secretion or uptake in trans-synaptic tracer protein, one would specifically need to be limited to a particular population of cells.

Because these *in vitro* issues are applicable to the *in vivo* situation, the *in vivo* use of the mice is not enabled.

In addition to the above reasons in the *in vitro* system for not being enabled for the *in vivo* system, the *in vivo* system is not enabled as follows. The specification teaches that transgenic mice comprising a pL7-tWGA construct and transgenic mice comprising a pOMP-tWGA construct were made (specification, Examples 2 and 3). While the specification teaches that these mice were made, the specification does not teach that these mice were crossed with mouse models of disease, wherein the crossed mice could be used for one of the intended uses indicated by the specification. Bates et al., 1997, Human Molecular Genetics, 6: 1633-1637, teach transgenic mouse models of Huntington's disease. Mice comprising a transgene construct that comprised an expanded uninterrupted allele of $(CAG)_{82}$ (PS-82) operably linked to a pcp2 (Purkinje cell specific promoter) resulted in five of six PS-82 lines that developed ataxia. Neuropathological analysis of the mice showed significant loss of the Purkinje cell population, with Bergmann glial proliferation, and shrinkage and gliosis of the molecular layer. Ectopic Purkinje cells were present in the molecular layer and occasionally the granular layer and the dendritic arrays also appeared to be abnormal (Bates, page 1634, 1st parag. under "Comparison with other CAG/POLYGLN mouse models). As this teaching applies to the instant invention and the use intended for the claimed mice, crossing the pL7-tWGA mice with the mouse model of Huntington's disease could not be used for intended use of 1), elucidation of causes for neurogenic diseases and for the establishment of medical treatment for those disease, as an artisan would see a significant loss of Purkinje cells. Whether or not an artisan would see any failed or remaining contacts of secondary neurons (e.g. in the thalamic ventrolateral nucleus, the

red nucleus, the vestibular nucleus or in the inferior olive (specification, figure 4)) is unclear and unpredictable as no cross between the transgenic WGA mice and the Huntington mice was made. Despite not knowing whether there is any remaining relationship between the Purkinje cells and its secondary cells, nothing about the localization of WGA in Purkinje cells provides insight as to the mechanism (i.e. the pathology) that caused the significant loss of Purkinje cells which would elucidate what caused the loss of these cells. Further, nothing about the localization of WGA in Purkinje cells provides insight into treatment of Huntington's disease. As such, the intended use of 1) is not clear for the claimed mice crossed with a model of disease. As for the intended use 3), the art teaches that neuronal regeneration is not routine in the art. For example, Legos et al., 2002, Expert Opinion of Investigative Drugs, 11: 469-482 teach that a wide variety of factors are involved in the treatment of spinal cord injury. Legos et al. teach that the degree of axonal response following neurotrophic factor treatment often varies and is largely determined by axonal type, the presence or absence of growth factor receptors, the type and extent of the injury and the local environment. Other determinants of axonal regrowth include the distance of the lesion from the neuronal cell bodies and the ability of the growing axon to find the appropriate target (Legos, et al. page 473, 1st parag. under "4.4 Growth Factors"). As this applies to the instant invention, while the claimed mice could be used to illustrate what neuronal connections are being made, the trans-synaptic tracer protein only illustrates, but does not provide any therapeutic effect on restoring injured pathways or helps form

compensatory pathways. As such, intended use 3) is not readily apparent. For these reasons, an artisan is not enabled to use the claimed mice.

Finally, with regard to using the cultured cells to give insight to screen for drugs that affect cell survival and maintenance, dendrite extension, synapse formation, various enzymatic activities, and/or neurotransmitter production, the art teaches that cultured cells are not representative of what occurs *in vivo*. As indicated above by Legos, et al., a wide variety of factors are involved in nerve regeneration that what is found in a cell culture does not necessarily translate to what is necessary *in vivo*. As such, the relationship between the intended use of the culture and as it applies to the *in vivo* animal model is not readily apparent.

For these reasons, these claims are rejected.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 6, 7 are newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 6 recites the limitation "said transgenic animal". There is insufficient antecedent basis for this limitation in the claim.

Claim 7 depends on a cancelled claim. For purposes of compact prosecution, claim 7 has been interpreted to read on claim 21.

Conclusion

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joanne Hama, Ph.D. whose telephone number is 571-272-2911. The examiner can normally be reached Monday through Thursday and alternate Fridays from 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, Ph.D. can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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JH

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PRIMARY EXAMINER